

Nested Case-Control Analysis of High Pesticide Exposure Events from the Agricultural Health Study

Michael C. R. Alavanja,^{1*} Nancy L. Sprince,⁴ Eugene Oliver,² Paul Whitten,⁴ Charles F. Lynch,³ Patricia P. Gillette,³ Nyla Logsdon-Sacket,³ and Craig Zwerling⁴

Background A nested case-control analysis of high pesticide exposure events (HPEEs) was conducted using the Iowa farmers enrolled in the Agricultural Health Study (AHS). **Methods** In the 12 months of the study, 36 of the 5,970 farmer applicators randomly chosen from the AHS cohort (six per 1,000 farmer applicators per year) met our definition of an HPEE, by reporting “an incident with fertilizers, weed killers, or other pesticides that caused an unusually high personal exposure” resulting in physical symptoms or a visit to a health care provider or hospital. Eligibility criteria were met by 25 HPEE cases and 603 randomly selected controls.

Results Significant risk factors for an HPEE included: poor financial condition of the farm which limited the purchase of rollover protective structures $OR = 4.6$ (1.5–16.6), and having a high score on a risk acceptance scale $OR = 3.8$ (1.4–11.2). Other non-significant factors were also identified.

Conclusions The limited statistical power of this study necessitates replication of these analyses with a larger sample. Nonetheless, the observed elevated odds ratios of an HPEE provide hypotheses for future studies that may lead to preventive action. *Am. J. Ind. Med.* 39:557–563, 2001. © 2001 Wiley-Liss, Inc.

KEY WORDS: pesticides; pesticide poisoning; accidental exposure; farmers; case-control study

INTRODUCTION

Pesticide spills, splashes, and immersions resulting from equipment maintenance, spot spraying, mixing and loading have resulted in relatively high pesticide exposure [Kross et al., 1992; Ogilvie et al., 1992]. Long-term adverse

health effects can result from pesticides exposures at levels associated with these events [O'Malley, 1997]. We have previously reported characteristics of persons who reported high pesticide exposure events (HPEE) from the Agricultural Health Study (AHS) [Alavanja et al., 1998, 1999], a large cohort of licensed restricted use pesticide applicators [Alavanja et al., 1996]. From these initial studies we observed that during their working life 14% of licensed pesticide applicators in the AHS had “an incident or experience while using a pesticide which caused an unusually high personal exposure.” Work practices more common among workers experiencing HPEEs include those who delayed changing clothing or washing after pesticide applications, those mixing pesticide application clothing with the family wash, applying pesticides within 50 yards of their well, and storing pesticides in their home. It was also more common for HPEEs to be seen among applicators who

¹Division of Cancer Epidemiology and Genetics, NCI, 6120 Executive Blvd.(EPS), Rm. 8000, Rockville, MD

²SAIC-Frederick, Science Applications International Corporation, Frederick, MD

³Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IW

⁴Department of Occupational and Environmental Health, College of Public Health, University of Iowa, Iowa City, IW

*Correspondence to: Michael C. R. Alavanja, Division of Cancer Epidemiology and Genetics, NCI, 6120 Executive Blvd.(EPS), Rm. 8000, Rockville, MD 20892.

E-mail: alavanjm@mail.nih.gov

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repaired their own pesticide application equipment and used showering facilities within the home, rather than special showers outside the home. We had the opportunity to extend these cross-sectional observations in a nested case-control study of HPEEs and traumatic injuries among private applicators in the Iowa portion of the AHS. The results of the HPEE analysis are reported here, while the results of the traumatic injury analysis will be reported separately.

METHODS

Case and Control Identification

On November 14, 1997 a screener questionnaire was mailed to 6,999 private pesticide-applicators randomly selected from among 30,009 licensed Iowa private pesticide applicators enrolled in the Agricultural Health Study. A second mailing was sent to non-respondents on December 2 and beginning on January 8, 1998 another attempt was made to contact all remaining non-respondents by telephone. A total of 6,115 private applicators completed a screener questionnaire and 5,970 indicated that they worked in an environment that met the census definition of farm by responding "yes" to the question, "Did this farm have a gross annual sales of agricultural goods of \$1,000 or more in the past 12 months?" Of these farmer applicators, 3,588 (60.1%) responded to the first mailing, 904 (15.1%) from the second mailing, and 1,478 (24.8%) from the telephone screener questionnaire. Thirty-six of these farmer applicators indicated that during the past 12 months, they had an incident or experience while using any type of pesticide or fertilizer which caused unusually high personal exposure and resulted in symptoms or a visit to a health care provider or hospital. In this study, this was the definition of an HPEE.

Case and Control Interview

Case and control interviews were performed using a Blaise Computer Assisted Telephone Interview system (CATI). Calls to subjects began on February 20, 1998 and ended on July 30, 1998. If subjects were not reached within eight call attempts, the study subject was classified as a non-respondent. On the basis of their response to the screener questionnaire 1149 applicators were selected to complete a CATI interview. To meet eligibility criteria for an HPEE case, during this interview farmer applicators had to indicate that they had an HPEE event during the same 12-month period covered by the screener questionnaire, and 2) not report an eligible traumatic injury during the same period. To be controls, farmer applicators had to indicate that they did not have an HPEE event and did not have a traumatic injury during the 12-month period covered in the screener questionnaire. Five hundred and twenty-one injury cases, 25

HPEE cases, and 603 randomly selected controls were selected to complete the CATI. Four hundred and seventy-three of the selected controls (78.4%) and 23 of 25 (92.0%) were successfully interviewed. Responses received from these controls and HPEE cases are the basis for this report. The case/control telephone interviews were taped with the study subjects' permission. Tapes were reviewed to assess and improve interview technique. In addition, an independent reviewer not otherwise associated with the study compared each tape to data entered into the database and corrected any data entry errors.

Interview Procedures/ Questionnaire

All eligible study subjects were offered \$10 to complete a CATI which was completed on average within 30 min. Trained interviewers administered the CATI. The interview consisted of questionnaire sections in the following order: demographics, work history for the past 12 months, injuries during the past 12 months, seriousness of injury, description of factors associated with the injury, HPEEs during the past 12 months, pesticide use during an HPEE, seriousness of the HPEE, description of factors associated with the HPEEs, personal medical history, mood and stress, smoking and alcohol consumption history, attitudes toward risk, farm finances and products, and safety training history. A description of several sections of this questionnaire is given below.

The Attitude Toward Risk section of the interview consisted of five primary questions derived from Harrel [Harrell, 1995]. All questions asked for the respondent to either agree or disagree to a statement and to rate each response as "somewhat" or "strongly" agree or disagree. The following statements were included: (1) "Farming is more dangerous than jobs in industry or manufacturing," (2) "Accidents are just one of the occupational hazards of farming that must be accepted if you are going to be in the business," (3) "Compared to other farmers I am very conscientious about avoiding accidents," (4) "During a normal work week, it's common for me, while doing farm work, to experience a number of 'close calls' that under different circumstances might have resulted in personal injury or property loss," (5) "To make a profit, most farmers take risks that might endanger their health." In our analysis, an answer of "disagrees" was tallied as a 0 for questions 1, 2, 4, and 5 and an answer of "agrees" was tallied as a 1. Agreeing with question 3 was tallied as a 0 while disagreeing was tallied as a 1. A cumulative score of 0–2 was considered "risk averse" vs. a score of 3–5 was considered "risk accepting."

The personal medical conditions section consisted of 26 questions including questions on eyesight and use of glasses or contact lenses, hearing and hearing aid use, arthritis and rheumatism, depression, heart disease and asthma. They

were derived from the 1992 Health and Retirement Survey questionnaire [Health and Retirement, 1992] and the 1994 National Health Interview Survey on Disability [National Health Interview Survey, 1994]. If the answer to any of the questions above was “yes”, follow-up questions were asked about the age of onset and whether a diagnosis by a doctor was made. Two other question sets were asked, namely (1) “Do you have any impairment or health condition that limits the kind or amount of work you can do?” (1A) “What health condition caused this limitation?”, and (2) “In the past 12 months, have you had any medical condition for which you have taken medicine regularly?” (2A) “What are these conditions? And, what are these medications?”

The farm finances and products section consisted of 25 questions concerning: the financial condition of the farm, whether the financial condition of the farm affected the purchase of safety equipment or time spent in various farm activities, the number of acres farmed, current farm debt as a percent of farm assets, and types of crops or animals raised on the farm.

The mood and stress section consisted of 24 questions which included the following: the 11-question Iowa form of the CES-D depression scale [Radloff, 1977; Kohout et al., 1993]; the four-item abbreviated Perceived Stress Scale [Cohen et al., 1983] with an added fifth question concerning changes in stress level over the last year; and the eight-item Epworth Sleepiness Scale [Johns, 1991].

The section on smoking and alcohol consumption consisted of seven questions on alcohol and three on cigarette smoking. The alcohol consumption questions assessed lifetime and current drinking status, usual amount of alcohol consumption, and the four CAGE questions used to assess alcoholism [Ewing, 1984]. The cigarette smoking questions were those used in the Third National Health and Nutrition Examination Survey [Third National Health and Nutrition Examination Survey, 1998–1994].

The pesticide use section asked 20 questions about the type of pesticides applications that were made, frequency of pesticide use, and the frequency of symptoms associated in time with pesticide use.

The safety training section consisted of 12 questions about source, date, and duration of training in any organized farm safety program or course. These questions did not specifically address safe pesticide application practices.

Data Analysis

Exact methods were used to compute odds ratios (OR) and 95% confidence intervals (CI) in univariate analysis [Breslow and Day, 1980; Cytel Software Corp., 1999] for all independent variables. Asymptotic methods were used to generate likelihood ratios. Independent-variables found related to an HPEE ($P \leq 0.1$) in the univariate analysis were ranked by likelihood ratios and entered singly into logistic

regression models. Exact and asymptotic logistic regression methods were used to estimate odds ratios (OR) and 95% CI in multivariate analysis (17,18). The dependent variable used was the dichotomous variable “yes” or “no” response to the question “Did you have an incident with fertilizers, weed killers, or other pesticides that caused an unusually high personal exposure” resulting in physical symptoms or a visit to a health care provider or hospital in the previous 12 months. The independent variables included those variables described above including demographics, work history for the past 12 months, description of factors associated with the injury, description of factors associated with the HPEEs, pesticide use, personal medical history, mood and stress, smoking and alcohol consumption history, attitudes toward risk, farm finances and products, and safety training history.

RESULTS

Thirty-six of the 5,970 farmer applicators who completed the screener questionnaire reported they had “an incident with fertilizers, weed killers, or other pesticides that caused an unusually high personal exposure resulting in physical symptoms” in the previous 12 months. This results in an incidence rate for an HPEE of six per 1,000 private applicators per year.

Twenty-three of the 25 farmer applicators that met eligibility criteria, elected to participate as HPEE cases in the nested case-control study. Of these, 8 (35%) had symptoms severe enough to warrant a visit to a health care provider (data not shown). All cases were white males. Table I lists the demographic characteristics of cases and controls. A larger fraction of cases (34.7%) compared to controls (18.8%) were 39 years old or less, but no meaningful difference was found between cases and control in years of education attained or marital status. Slightly fewer cases (78.3%) than controls (90.0%) lived on a farm, but the difference was not statistically significant. Cases and controls had similar occupations during the past 12 months. More cases (95.6%) than controls (88.4%) spent a majority of their time farming.

All significant odds ratios from a univariate analysis using exact methods are presented in Table II, along with nonsignificant odds ratios above 1.8 where at least 2 cases were involved. Private pesticide applicators whose farm was in poor financial condition causing them to defer purchase of rollover protective structures OR = 4.5 (1.6–12.5), those who had a high cumulative “risk acceptance” score OR = 3.3 (1.4–8.0), and those who had an “off the farm job” OR = 2.6 (1.1–6.2) were at significantly greater risk of an HPEE than were farmer applicators who did not have these characteristics. Risk factors elevated for an HPEE, but not statistically significant, included “bad eyesight” OR = 3.0 (0.8–8.9), full time farm workers OR = 2.7 (0.5–57.7), farmers who sought help from others with their farm

TABLE I. Demographic Characteristics of 23 High Pesticide Exposure Event Cases and 473 Controls Among Private Pesticide Applicators in the Agricultural Health Study in Iowa

Characteristics	Cases (%)	Controls (%)
Age		
20–29	3 (13.0)	9 (1.9)
30–39	5 (21.7)	82 (16.9)
40–49	7 (30.4)	167 (34.5)
50–59	3 (13.0)	113 (23.3)
≥ 60	5 (21.7)	113 (23.3)
Education		
< 12	2 (8.7)	17 (3.5)
12	11 (47.8)	257 (53.1)
> 12	10 (43.5)	209 (43.2)
Marital status		
Married	21 (91.3)	439 (90.7)
Separated/divorced	1 (4.3)	14 (2.9)
Never married	0	24 (5.0)
Where do you live		
On the farm	18 (78.3)	440 (90.0)
Rural-non-farm	1 (4.3)	9 (1.8)
Urban	4 (17.4)	40 (8.2)
Occupation past 12 months		
Full time farmer	18 (78.3)	379 (77.5)
Part time farmer	4 (17.4)	80 (16.4)
Retired farmer	1 (4.3)	22 (4.5)
Hired farmer	0	6 (1.2)
Spent 50% or more time farming in the past 12 months	22 (95.6)	428 (88.4)

operation OR = 2.7 (0.7–17.3), younger age (≤ 39 years vs. > 39 years) OR = 2.5 (0.96–6.0), those who had an elevated score on the CES-D depression scale OR = 2.4 (0.7–7.0), those who felt “bad or guilty” about drinking alcohol 2.3 (0.6–6.8), farmer applicators who had “trouble hearing” OR = 2.2 (0.9–5.3), those who owned farms of 500 or more acres OR = 2.2 (0.9–5.4), those whose farms were in poor financial condition (farmer’s response to questionnaire) OR = 2.1 (0.8–5.3), and those who were diagnosed with asthma OR = 2.0 (0.3–7.8) or depression OR = 1.9 (0.3–7.4). Attendance at farm safety programs given at a variety of venues (i.e., extension service, agricultural vocational courses, seed wholesalers), other medical conditions or farm type was not related to diminished or excess risk of high pesticide exposure events.

Six independent variables (i.e., ‘poor financial condition of farm defers purchase of ROPS,’ ‘high risk acceptance,’ ‘bad eyesight,’ ‘trouble hearing,’ ‘off the farm job,’ and ‘younger age’) related to an HPEE ($P \leq 0.1$) in the univariate analysis in Table III were ranked by likelihood

ratios (data not shown) and entered singly into logistic regression models. (Table III). All six independent variables remained significant at the $P \leq 0.1$ level. Private pesticide applicators whose farm was in poor financial condition causing them to defer purchase of rollover protective structures OR = 4.6 (1.5–16.6) and those who had a high cumulative “risk acceptance” score OR = 3.8 (1.4–11.2) were at significantly greater risk of an HPEE (in the multivariate analysis using exact methods) than were farmer applicators who did not have these characteristics. Risk factors elevated for an HPEE but not statistically significant in the multivariate analysis using exact methods included: “bad eyesight” OR = 2.8 (0.6–10.1), “trouble hearing” OR = 2.5 (0.9–7.3), and an off the farm job OR = 2.5 (0.9–7.0). Younger age (i.e., ≤ 39 years) had the lowest likelihood ratio score and was therefore the last to be added to the model. LogXact failed to produce exact estimates for this variable and asymptotic methods were used to estimate an OR = 2.6 (0.9–7.3). No single pesticide was responsible for more than four HPEE cases (data not shown in table).

Among the 23 cases, the most common symptom associated with an HPEE was headache (54.2%), followed by skin irritation (36.4%), nausea or vomiting (34.8), dizziness (27.3%), feeling excessively tired (26.1%), chest discomfort (21.7%), difficulty in breathing (21.7%), nervousness or depression (17.4%), followed by eye irritation (13%) and twitching and jerking of the arms and legs (13%). Other symptoms were reported by 30.4% of the HPEE cases (Table IV).

DISCUSSION

We estimate that six per 1,000 farmer applicators per year in Iowa experienced a high pesticide exposure event during the period from 1997–1998, resulting in physical symptoms or a visit to a health care facility. These symptoms most frequently included headaches, skin irritation, nausea or vomiting, dizziness, and feeling excessively tired and sometimes the symptoms included chest discomfort, breathing difficulties, nervousness or depression, eye irritation, jerking or involuntary movements of the arm and legs. The HPEEs sometimes resulted in a large variety of less frequently reported symptoms. Among those with symptoms, approximately 35% sought medical treatment from a health care provider. The long-term consequences of these events are not well understood, but with the relatively high doses involved, chronic disease is possible [O’Malley, 1997]. Previously we have determined that 14% of the Agricultural Health Study cohort has experienced an HPEE during their working lifetime [Ogilvie et al., 1992] and since this experience may be reflective of exposures in other agricultural populations we are interested in examining both the determinants and, in later studies, the health consequences of these events.

TABLE II. Unadjusted Odds Ratio^a and 95% CI for Factors Associated with High Pesticide Exposure Events Among Farmer Pesticide Applicators in the Agricultural Health Study in Iowa

Variable	Study subjects with variable	Study subjects with variable and HPPE	Odds ratio	95% CI
Financial condition of farm reported as poor: limiting purchase of rollover protective equipment	198	16	4.5	1.6–12.5
High risk acceptance	146	13	3.3	1.4–8.0
Off farm job	170	13	2.6	1.1–6.2
Bad eyesight	35	4	3.0	0.8–8.9
Full time farmer	443	22	2.7	0.5–57.7
Gets some help with farm work	395	21	2.7	0.7–17.3
Younger age (≤ 39 vs. > 39)	92	8	2.5	0.96–6.0
Depression by (CES-D) depression index (16 or more)	42	4	2.4	0.7–7.0
Felt bad or guilty about drinking alcohol	44	4	2.3	0.6–6.8
Trouble hearing normal conversation	115	9	2.2	0.9–5.3
Farm size large (≥ 500 acres vs. < 500 acres)	247	15	2.1	0.9–5.6
Financial condition of farm rated poor by farmer	102	7	2.1	0.8–5.3
Asthma	24	2	1.9	0.3–7.8
Diagnosis of depression	25	2	1.9	0.3–7.4

^aOdds ratios and 95% CI calculated with StatXact v 3 for Windows. Univariate test for each variable.

Thirteen of 23 private applicators reporting an HPEE had a high risk acceptance score, resulting in an odds ratio of 3.8. Sixteen of 23 farmer applicators reported that the poor financial condition of the farm influenced their decision to defer purchase of rollover protective structures resulting in an odds ratio of 4.6. The prevalence of these characteristics among cases and the large relative risk associated with both characteristics among farmer applicators suggest they are associated with a large majority of the events. These two risk factors may be interrelated and there may be statistical interaction between the two which the small size of our sample could not demonstrate. Although it seems clear that individuals who believe they must take risks in order to have their farm operation remain economically viable and those who deferred purchase of a piece of safety equipment because of the poor financial condition of their farm will have more injury and HPEEs, it is not clear how best to reduce the risk among these individuals. The underlying determinant of the attitude toward risk may be the narrow profit margin of the farm,

which may be amenable, in part, to an economic solution. On the other hand, this attitude toward risk may be a behavioral characteristic of the person unaffected by economic intervention. Similarly, 13 of 23 applicators reporting an HPEE had an off the farm job. While the risk associated with the job off the farm was not statistically significant, 13 of 23 applicators with an HPEE had such jobs and the multivariate risk (odds ratio) associated with them was 2.5. The reasons to take an off the farm job may vary, but they may be part of the same constellation of economic factors which make it necessary for some farmers to put off purchase of some types of safety equipment. More research on larger samples of farmers will permit a more comprehensive investigation of these issues, particularly the identification of individual pesticides that may be associated with an HPEE. Additionally, a larger sample size will permit analysis of the potential interaction of economic and behavior determinants of injury and HPEEs.

The small number of events reported limited the statistical power of our study and necessitates replication

TABLE III. Adjusted Odds Ratios^a and 95% CI for Factors (Listed by Magnitude of Odds Ratio) Associated With High Pesticide Exposure Events Among Farmer Applicators in the Agricultural Health Study in Iowa

Variable	Odds ratio	95% CI
Financial condition of farm reported poor as: limiting purchase of rollover protective equipment	4.6	1.5 – 16.6
Risk acceptance high	3.8	1.4 – 11.2
Bad eyesight	2.8	0.6 – 10.1
Young age (≤ 39) ^b	2.6	0.9 – 7.3
Off the farm job	2.5	0.9 – 7.0
Trouble hearing	2.5	0.9 – 7.3

^aAdjusted odds ratios and 95% CI calculated with LogXact v 1.2. Adjustment includes all other variables in Table III.

^bYoung age was the sixth variable to be added to the model. LogXact failed to produce exact estimates and asymptotic estimates are reported for this variable.

of these analyses with a larger sample. Nonetheless, the observed elevated odds ratio of an HPEE associated with bad eyesight, trouble hearing, and younger age of the farmer applicator (≤ 39) experiencing an HPEE may eventually lead to preventive action. Bad eyesight has previously been reported to be a risk factor for injury in both agricultural and industrial populations [Zwerling et al., 1995], but it has not been identified as a risk factor for high exposure to pesticides. In this study, the reason for the self-reported poor eyesight “with your glasses or contact lens” was not requested. Some eye conditions resulting in poor eyesight are amenable to correction and others are not, determining the specific eye conditions associated with these events is a reasonable next question for research. Similarly, quantifying the degree of hearing loss and characterizing the HPEE scenarios involving farmers with hearing loss are reasonable next questions for research, while evaluating the hearing and visual acuity of pesticide applicators seeking a restricted use license may be sound public health policy. The reason for observing elevated risks of an HPEE among younger farmers is not clear. Inadequate experience with farming is one possibility, but it also may be that younger farmers are less able to afford safety equipment and may also be more inclined to take risks to keep their farm operation economically viable. With only eight farmers in the high risk age group in this study, it was not possible to further elucidate covariates of risk related to age. We did not observe an association between safety training and high pesticide exposure episodes. Our results cannot address the effectiveness of training in safe pesticide application procedures, since the safety training questions did not refer specifically to training in pesticide application.

A major strength of this study is that it is nested within the Iowa portion of the Agricultural Health Study cohort of

TABLE IV. Symptoms Associated with High Pesticide Exposure Events Among Farmer Applicators in the Agricultural Health Study in Iowa

Symptoms	Yes	No	Yes (%)
Headaches	12	11	54.2
Skin irritation	8	14	36.4
Nausea or vomiting	8	15	34.8
Dizziness	6	16	27.3
Excessively tired	6	17	26.1
Chest discomfort	5	18	21.7
Difficulty in breathing	5	18	21.7
Nervous or depressed	4	19	17.4
Eye irritation	3	20	13.0
Twitching, jerking, or involuntary movements of arms or legs	3	20	13.0
Other symptoms	7	16	30.4

restricted use farmer pesticide applicators, thereby making it possible to estimate the incidents of HPEEs within a well-characterized farm population. The comprehensive questionnaires used identified a broad spectrum of risk factors and because of the longitudinal design of the Agricultural Health Study, it will be possible to follow up hypotheses generated here with additional targeted investigations. However, the study does have several limitations as well. First, as we have stated earlier, the small size of the HPEE case population limits the extent of the analyses that can be performed. Some factors such as feeling guilty about alcohol consumption, symptoms of depression, operating a farm over 500 acres, and asthma were associated with non-significantly elevated risk in the univariate analyses and deserve greater scrutiny in a larger investigation. In addition, a larger sample size will help with more detailed investigations of HPEE scenarios and interactions, which would make recommendations for public policy more specific. Second, because the data on risk factors and occupational HPEEs were collected in the same survey, there is the possibility of recall bias. The occurrence of an HPEE with symptoms or a visit to a doctor or hospital could make case subjects more likely to remember risk factors. However, the amount of recall bias should be reduced since all risk factor questions are posed in a follow-up questionnaire after the occurrence of an HPEE has been established in the initial screener questionnaire. Third, since all HPEEs and symptoms resulting from the HPEEs were self-reported, it is possible the farmers are less likely to report all such events, resulting in an under estimation of the actual incidence. While this study may underestimate the total number of HPEEs occurring in the farm population we did observe HPEEs which did not result in visits to doctors or hospital and we have no reason to believe the observed

risk factors would differ greatly for non-reported HPEEs. While our study cannot demonstrate conclusive casual associations between the risk factors and HPEEs, the results of this exploratory study provide hypotheses for future research, which may result in fewer occupationally related pesticide poisonings.

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